L Number	Hits	Search Text	DB	Time stamp
2	666	plating adj liquid	USPAT	2003/06/09 14:49
3	0	(evaporative adj light adj scattering adj detector) and (plating adj liquid)	USPAT	2003/06/09 14:49
4	75043	210/$.ccls.	USPAT	2003/06/09 14:50
5	26	(evaporative adj light adj scattering adj detector) and 210/$.ccls.	USPAT	2003/06/09 14:58
6	1	ultraviolet same (differential adj refraction)	USPAT	2003/06/09 15:02
7	0	(evaporative adj light adj scattering adj detector) same (differential adj refraction)	USPAT	2003/06/09 15:04
8	17	(evaporative adj light adj scattering adj detector) same ultraviolet	USPAT	2003/06/09 15:32
9	22	evaporative adj mass adj detector	USPAT	2003/06/09 15:32
10	0	(plating adj liquid) and (evaporative adj mass adj detector)	USPAT	2003/06/09 15:32
11	194634	chromatogra$4	USPAT	2003/06/09 15:33
12	124	(evaporative adj light adj scattering adj detector) and chromatogra$4	USPAT	2003/06/09 15:33
13	7	(evaporative adj light adj scattering adj detector) same quantif$6	USPAT	2003/06/09 15:34
1	132	evaporative adj light adj scattering adj detector	USPAT	2003/06/09 15:35

US-PAT-NO: 6210571

DOCUMENT-IDENTIFIER: US 6210571 B1

TITLE: Automated on-line evaporating light scattering detection to quantify isolated fluid sample compounds in microtiter plate format

DATE-ISSUED: April 3, 2001

US-CL-CURRENT: **210/198.2**, **210/656** , **210/659** , 422/70 , 73/61.52

APPL-NO: 09/ 415541

DATE FILED: October 8, 1999

PARENT-CASE:

CROSS-REFERENCES TO RELATED APPLICATION(S)

The present application is a divisional patent application which claims the benefit and priority of U.S. patent application Ser. No. 09/219,083 filed Dec. 22, 1998, now U.S. Pat. No. 6,077,438 the full disclosure of which is incorporated herein by reference for all purposes.

---------- KWIC ---------

Abstract Text - ABTX (1):

Single pass methods and systems for measuring the total masses of individual compounds present in fluid samples in real time, and particularly for fluid samples prepared in microtiter plate format are provided. Individual compounds are isolated by fluid separation column (14). Portions of the individual

compounds isolated by column (14) are analyzed by mass spectrometer (16), which determines their concentration on the basis of their molecular weights, and an **evaporative light scattering detector** (24), (which determines the total masses of each of the isolated compounds passing therethrough). Total collected masses of the individual compounds are calculated by determining the amount and portion of the isolated compounds diverted into **evaporative light scattering detector** (24) during a period of fraction collection.

Brief Summary Text - BSTX (8):

The present invention provides methods and systems for measuring the total masses of individual compounds present in fluid samples, and is particularly well adapted for use with fluid samples prepared in microtiter plate format. In a preferred aspect, the individual compounds arc isolated by fluid separation systems including high performance liquid chromatography columns and supercritical fluid columns. Small portions of the individual compounds isolated by fluid separation are then analyzed by a mass spectrometer, (which determines the compound molecular weight), and by an **evaporative light scattering detector,** (which determines the total masses of each of the isolated compounds passing therethrough). The present invention provides a single pass system which measures the masses of the individual compounds diverted into fraction collectors in real-time, as follows.

Brief Summary Text - BSTX (9):

The signal generated by the mass spectrometer is used to determine the interval of time during which fraction collection is to be carried out. The signal generated by the **evaporative light scattering detector** is used to

determine the total amount of mass diverted therethrough during the interval of time during which fraction collection is carried out. By knowing the portion of fluid sample diverted into the **evaporative light scattering detector,** (relative to the portion of fluid sample which is directed to fraction collection), it is then possible to calculate the total masses of each of the individual isolated compounds as they are fraction collected.

Brief Summary Text - BSTX (18):

In addition, a very small portion, (typically on the order of 1%), of the sequentially eluted isolated compounds in the fluid sample are diverted into an **evaporative light scattering detector**. The **evaporative light scattering detector** generates a chromatographic signal of the sequentially eluted isolated compounds which is proportional to the total masses of the various compounds passing therethrough. An advantage of evaporative light scattering detection is that it is mass dependent and will tend to be generally uniform over a wide range of different chemical structures. Accordingly, a single calibration curve can be generated between masses passing through the **evaporative light scattering detector** and its signal output.

Brief Summary Text - BSTX (22):

Initially, a calibration curve between the mass passing through the **evaporative light scattering detector** and the signal generated by the **evaporative light scattering detector** is determined. Such a calibration curve can be established by determining the signal output when passing known masses through the light scattering detector.

Brief Summary Text - BSTX (25):

In addition, the present system can be adapted to perform simultaneous real time mass determinations of a plurality of fraction collected samples, wherein a plurality of simultaneously eluted fluid samples can be analyzed by the **evaporative light scattering detector** and the mass spectrometer. In various aspects of the invention, parallel simultaneously eluted fluid samples pass through a switching valve such that each of the samples can be analyzed by the **evaporative light scattering detector** and the mass spectrometer in turn. In alternate aspects, parallel light scattering detection is performed by a plurality of lasers or with a single laser having its beam sequentially directed towards the various samples eluted in parallel.

Detailed Description Text - DETX (7):

The amounts of flow diverted to splitters 21 and 22, and the volume of connecting tubes 32, 34 and 36, is set such that eluting compounds from column 14 reaches each of mass spectrometer 16, **evaporative light scattering detector** 24 and microtiter plate fraction collector 18 at the same time. Accordingly, at the moment in time when mass spectrometer 16 signals that fraction collection of a particular isolated compound reaching mass spectrometer 16 should commence, the same particular isolated compound will be reaching liquid handling robot 20 such that it can be diverted into fraction collector microtiter plate 18. Therefore, compound purification can be performed in real time.

Detailed Description Text - DETX (8):

A small portion, (typically on the order of 1%), of the separated fluid sample is diverted by splitter 22, (which preferably

comprises a Valco Splitter
Tee), towards an **evaporative light scattering detector** 24.
Light scattering
detector 24 measures the total mass of the fluid sample
passing therethrough on
the basis of the amount of light scattered per unit mass
passing therethrough.
An advantage of light scattering detection is that a signal
which is mass
dependent within a narrow range of response factors is
produced. As such, the
total mass of the fluid sample is determined without regard
to the way in which
various particles absorb light, which would in turn depend
upon the structural
nature of the particle, with different chromophores having
a wide range of
response factors, making system calibration difficult.

Claims Text - CLTX (4):
an **evaporative light scattering detector** for determining
the total masses of
the isolated compounds passing therethrough;

Claims Text - CLTX (5):
a second splitter for diverting a second portion of the
fluid sample into
the **evaporative light scattering detector**; and

Claims Text - CLTX (21):
a switching valve for sequentially diverting the
isolated compounds from
each of a plurality of fluid separation devices into the
**evaporative light
scattering detector**.

Claims Text - CLTX (22):
9. The system of claim 1, wherein the **evaporative light
scattering detector**
further comprises;

Current US Original Classification - CCOR (1):
210/198.2

Current US Cross Reference Classification - CCXR (1):
210/656

Current US Cross Reference Classification - CCXR (2):
210/659

US-PAT-NO: 5670054

DOCUMENT-IDENTIFIER: US 5670054 A

TITLE: Method and system for identification, purification, and quantitation of reaction components

DATE-ISSUED: September 23, 1997

US-CL-CURRENT: **210/656**, **210/143** , **210/198.2** , **210/659**

APPL-NO: 08/ 626290

DATE FILED: April 4, 1996

---------- KWIC ---------

Brief Summary Text - BSTX (12):

While there are several mass-sensitive detectors compatible with HPLC, (e.g., refractive index, flame ionization, etc.) they are not practical for use in the rapid quantitation of combinatorial libraries. For example, refractive index detection is incompatible with gradient elution in HPLC and flame ionization detectors require the use of cumbersome interfaces that can be difficult to maintain. **Evaporative light scattering detectors** (ELSD), commercialized within the last ten years, traditionally have been used to detect and quantitate compounds that absorb poorly in the UV (e.g., phospholipids, alkyl surfactants, lipids, etc.). The use of evaporative light scattering detection for the analysis of combinatorial libraries by HPLC has been reported. The ELSD measures the intensity of scattered light generated by a desolvated, nebulized band of solute particulates passing

through the beam of
a fixed light source. In general, the response of the ELSD is proportional to
the mass of the component eluting from the column.
Evaporative light scattering detectors are compatible with high throughput gradient HPLC methods.
Unlike other mass-sensitive detectors (e.g., refractive index, etc.) the
response of the ELSD is logarithmic rather than linear.

Detailed Description Text - DETX (20):
The quantitation may be performed on a sample having had the mobile phase
stripped away and reconstituted, or alternatively, is performed on the same
fraction following collection using an analytical HPLC equipped with an
evaporative light scattering detector. Suitable **evaporative light scattering detectors** for quantitation include the Varex (Burtonsville, Md.) Model MK-III
and the Sedex Models 55 and 65 detectors available from Sedere, Alfortville,
France. In the latter case, the total sample volume needed for calculation of
sample concentration could be determined by the system software as the product
of the chromatographic eluent's volumetric flow rate and sample collection
time.

Current US Original Classification - CCOR (1):
210/656

Current US Cross Reference Classification - CCXR (1):
210/143

Current US Cross Reference Classification - CCXR (2):
210/198.2

Current US Cross Reference Classification - CCXR (3):
210/659

US-PAT-NO: 6406633

DOCUMENT-IDENTIFIER: US 6406633 B1

TITLE: Fraction collection delay calibration for liquid chromatography

DATE-ISSUED: June 18, 2002

US-CL-CURRENT: 210/659, 210/143 , 210/198.2 , 210/85 , 436/161 , 73/61.57

APPL-NO: 09/ 611148

DATE FILED: July 6, 2000

PARENT-CASE:

CROSS REFERENCE TO RELATED APPLICATION(S)

This is a divisional of application Ser. No. 09/393,595 filed on Sep. 10, 1999, now U.S. Pat. No. 6,106,710.

---------- KWIC ---------

Brief Summary Text - BSTX (10):

In some embodiments the destructive detector is a mass spectrometer or an **evaporative light scattering detector** or an electrochemical detector. In some embodiments each or both of the first and the second non-destructive detector is an optical detector, such as a UV-Vis absorption detector, a fluorescence detector, or a refractive index detector. In some embodiments the conduits comprise tubing or channels formed in a solid substrate; where an optical detector is employed as a nondestructive detector the conduit preferably is

constructed of a material that permits transmission of the wavelength (UV, visible) or wavelengths employed in the detection.

Brief Summary Text - BSTX (11):

In some embodiments the fraction collection apparatus further includes a fourth conduit connected at its upstream end to a third outlet from the flow splitter and connected at its downstream end to a quantitative detector. In still other embodiments having a fourth conduit connected at its downstream end to a quantitative detector, the apparatus further includes a second splitter having an inlet and a first outlet connected inline in either the second conduit or the third conduit, and a second outlet connected to the upstream end of the fourth conduit. In some embodiments the quantitative detector includes an **evaporative light-scattering detector** or a nitrogen-sulfur detector.

Detailed Description Text - DETX (4):

The destructive analytical detector 18 may be a mass spectrometer, an **evaporative lights-scattering detector** ("ELSD"), or an electrochemical detector.

Detailed Description Text - DETX (14):

Referring now to FIGS. 4-6, there are shown diagrammatically parts of system flow paths generally indicated at 40, 50, 60, in which an additional conduit is provided, to direct a part of the eluent stream to a quantitative detector 70. In each of these Figs., the part of the system upstream from the splitter may be configured, for example, as in either of FIG. 1 or 2, and like parts are identified with like reference numerals. In the embodiment of FIG. 4, the splitter 44 has a third outlet, and the additional conduit

42 is connected at its upstream end to the third outlet and at its downstream end to the quantitative detector 70. In the embodiment of FIG. 5, an additional splitter 54 is interposed in conduit 26 between splitter 14 and flow detector 15. Splitter 54 receives eluent from the splitter 14 and directs the eluent flow in part by way of conduit 26 to the fraction collector 16 and in part by way of an additional conduit 56 to the quantitative detector 70. Accordingly, in such embodiments the portion of the eluent stream that is directed from the splitter toward the fraction collector 16 is diverted to the quantitative detector 70. In the embodiment of FIG. 6, an additional splitter 64 is interposed in conduit 28 between splitter 14 and destructive analytical detector 18. Splitter 64 receives eluent from the splitter 14 and directs the eluent flow in part by way of conduit 28 to the destructive analytical detector 18 and in part by way of an additional conduit 66 to the quantitative detector 70. Accordingly, in such embodiments the portion of the eluent stream that is directed from the splitter toward destructive analytical detector 18 is diverted to the quantitative detector 70. The quantitative detector is a destructive detector, and may be, for example, an **evaporative light-scattering detector** or a nitrogen-sulfur detector; such detectors are known in the chromatography art. The respective components of the separated sample typically will have different arrival times at the quantitative detector 70, at the destructive detector 18 and at the fraction collector 16, as described generally above with reference to FIGS. 1 and 2. A delay interval between the time of arrival at the quantitative detector 70 and the time of arrival at any of the other detectors can be determined and calibrated in a similar fashion, to provide

for association of
the quantitative data generated at the quantitative
detector with a particular
sample component.

	Type	L #	Hits	Search Text	DBs	Time Stamp	Comments
1	BRS	L2	666	plating adj liquid	USPAT	2003/06/09 14:49	
2	BRS	L3	0	1 and 2	USPAT	2003/06/09 14:49	
3	BRS	L4	75043	210/$.ccls.	USPAT	2003/06/09 14:50	
4	BRS	L5	26	1 and 4	USPAT	2003/06/09 14:58	
5	BRS	L6	1	ultraviolet same (differential adj refraction)	USPAT	2003/06/09 15:02	
6	BRS	L7	0	(evaporative adj light adj scattering adj detector) same (differential adj refraction)	USPAT	2003/06/09 15:04	
7	BRS	L8	17	(evaporative adj light adj scattering adj detector) same ultraviolet	USPAT	2003/06/09 15:32	
8	BRS	L9	22	evaporative adj mass adj detector	USPAT	2003/06/09 15:32	
9	BRS	L10	0	2 and 9	USPAT	2003/06/09 15:32	
10	BRS	L11	194634	chromatogra$4	USPAT	2003/06/09 15:33	
11	BRS	L12	124	1 and 11	USPAT	2003/06/09 15:33	
12	BRS	L13	7	(evaporative adj light adj scattering adj detector) same quantif$6	USPAT	2003/06/09 15:34	
13	BRS	L1	132	evaporative adj light adj scattering adj detector	USPAT	2003/06/09 15:35	

	Error Definition	Errors
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